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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/519,148	LIPSHUTZ ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Acknowledgement is made of receipt of response on 19 November to the Office action of 13 June 2002. No amendment to the claims or specification was found to accompany the response.

2. The status of the claims is as follows:

- Claims 1-79 have been cancelled.
- Claim 80 and 93 are thrice amended
- Claim 106 and 107 are amended.
- Claims 81-92, 94-105, 108, and 109 are pending.

Drawings

3. The corrected or substitute drawings were received on 24 February 2003.

Oath/Declaration

4. The following is a quotation of the appropriate paragraph of 37 CFR 1.67(b) that form the basis for the objection under this section made in this Office action:

> A supplemental oath or declaration meeting the requirements of § 1.63 must be filed when a claim is presented for matter originally shown or described but not substantially embraced in the statement of invention or claims originally presented or when an oath or declaration submitted in accordance with § 1.53(f) after the filing of the specification and any required drawings specifically and improperly refers to an amendment which includes new matter. No new matter may be introduced into a nonprovisional application after its filing date even if a supplemental oath or declaration is filed. In proper situations, the oath or declaration here required may be made on information and belief by an applicant other than the inventor.

As a result of amendment(s) to the claim(s), the pending claims no longer substantially embrace the invention as set forth in the statement of the invention and/or in the original claims. Accordingly, applicant is required to file a supplemental oath or declaration in response to this Office action.

Specification

5. The specification is objected to as documents have been improperly incorporated by reference. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

6. The disclosure is objected to because of the following informalities:

a. At page 20, 46 of the specification it appears that a symbol to define depth is missing for it would appear that wells of 250 and 500 meters in depth were used.

b. The specification makes reference to US Patent applications but the current status of same is not indicated. See, e.g., pages 15, 18, 22, and 35.

c. At page 21, line 4, there appears "hese." Perhaps applicant had intended --these--.

Appropriate correction is required.

7. The title of the invention, as provided in the amendment to same received 24 February 2003, is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. It is noted with particularity that none of the claims are drawn to a device yet the title indicates that the invention lies in a device.

Claim Objections

8. A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim.

A claim, which depends from a dependent claim, should not be separated by any claim that does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

9. Claims 119-124 are objected to because of the following informalities: There are two claims numbered "119" yet the text of the claims is different. As a result, the numbering of the claims from the second occurrence of "119," through 124 is incorrect. Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80-108 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

11. Independent claims 80, 93, 106, and 107 are all drawn to "[a] method of analyzing a sample." Each of said claims require the detection and evaluation of a signal through the use of confocal microscopy, and in the case of claims 80 and 93, hybridization is to have taken place prior to the signal being detected and evaluated. In accordance with the recited method steps, and using claim 80 as an example for the remaining independent claims, one is to perform two method steps prior to performing said confocal microscopy. One of the method steps is to be performed in a first chamber and the second method step is to be performed in a second chamber. The first method step can be "a preparative reaction, an analysis reaction, sample acquisition, DNA extraction, amplification, IV transcription or labeling" and the second method steps can be "a preparative reaction, an analysis reaction including hybridization, sample acquisition, DNA extraction, amplification, IV or labeling." In view of the choices presented, the claims are considered to encompass performing "sample acquisition" in the first chamber and "DNA extraction" in the second chamber and there never take place any hybridization reaction, much less the incorporation of a label that would produce a signal that would be detected by confocal microscopy being practiced from without the device when extracted and unlabeled and unhybridized DNA is within the device. Other combinations, still not requiring any hybridization or any label, are also encompassed.

12. The specification does not set forth a reproducible procedure whereby the unhybridized and unlabeled can be detected and a signal produced from that which is incapable of producing a signal, can in turn be analyzed such that any meaningful determination be made about the sample under investigation.

The specification discloses three examples: Example 1- Acoustic Mixing (pages 44-45), Example 2- RNA Preparation Reaction in Miniaturized System (pages 45-46), and Example 3- PCR Amplification in Miniaturized System (pages 46-47). None of thee example disclose starting materials and reaction conditions where a first reaction chamber and second reaction chamber are used to perform the defined reactions, and to then perform confocal microscopy on a hybridized sample and then make any analysis of the results. In short, it appears that applicant is trusting in the ability of the public to determine the operational parameters so to enable the claimed method and related device. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is

> no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

The level of skill in the art is considered to be high, on par with those that hold a Ph.D. in biochemistry and have several years of laboratory experience. Such high level of experience, however, is offset by unpredictability in the art. As presently worded, the claimed methods are considered to encompass performing and analysis of physiological and chemical conditions which are recognized as being unpredictable. In support of this position, attention is directed to the decision of *Vas-Cath Inc. v. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

> This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 USC 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Additionally, the claimed method relates to the use of devices that have fluid connections, which present additional issues of enablement. The art recognizes numerous difficulties associated with junctions in a device intended for fluid manipulation. As set forth in Shartle et al., (US Patent 5,230,866):

> A number of factors contribute to the instability of the junction. For example, variations in the sample physical properties (such as density, viscosity, hematocrit, microheterogeneity, surface tension, and contact angle with housing wall) can affect both the forward pressure acting to favor flow and the backpressure available at the stop-flow

> junction to stop flow. Density controls the hydrostatic pressure at the junction. Surface tension and contact angle determine the pressure that the junction can exert in opposition to flow. Viscosity determines the rate at which the sample moves to the junction and therefore the excess back pressure (over that necessary for an equilibrium state) required to prevent the momentum of the sample from breaking through the junction. Hematocrit of blood sample affects both viscosity and density. Microheterogeneity has an impact on local properties at the junction, which can vary significantly from the bulk properties of the sample. Other variations include sample volume, which affects hydrostatic pressure by varying the height of the upper sample surface above the junction; method of sample application by different uses [*sic*; users] (or by the same user at different times); variation from lot to lot of the physical properties, such as contact angle with a standard liquid, of the housing out of which the diluter is made; variations in the size and shape of the junction arising during manufacturing, such as can be caused by plastic "burrs" at corners and edges, and local external factors, such as mechanical vibrations caused by nearby machinery of the diluter from a horizontal operating position.

The specification is effectively silent as to how these art-recognized issues are to be overcome.

13. The art to which the invention relates, i.e., nucleic acid array art and hybridization art, has advanced to the point that certain problematic areas have been identified. In support of this position as it relates to the manufacture and use of oligonucleotide arrays, US Patent 6,077,674 (Schleifer et al.) addresses certain highly problematic areas:

> While in situ synthesis is a very flexible means for producing DNA arrays, the fidelity or percentage of full-length oligonucleotides synthesized within a feature on the array is less than 100 percent. An ideal array will have only full-length oligonucleotides attached to each feature. The ideal array promotes accuracy in hybridization experiments or assays or target biological materials. If the fidelity of an in situ generated array is less than 100 percent, it typically has non full-length oligonucleotides within a feature that usually consists of shorter lengths of the correct sequence, and to a lesser degree, incorrect sequences. Typical DNA coupling efficiencies are around 97 to 99 percent for the standard phosphoramidite chemistry. For oligonucleotides that are 25 nucleotides in length, these efficiencies result in only 46 to 77 percent full-length oligonucleotides contained within a feature (0.97^{25} to 0.99^{25}). This loss of fidelity can cause chemical noise in hybridization conditions. The loss of fidelity can also lead to difficulty in interpreting the data.
>
> Photolithography is a method used by Affymetrix in California to produce in situ arrays using procedures that are similar to those used in the semi-conductor industry. In procedure described by Fodor et al. from Affymetrix U.S. Pat. No. 5,405,783, a photo-deprotection step is used where the protecting group on the phosphoramidite is removed by exposing a photosensitive protecting group to light. Four photo masks are used to

> create patterns to de-protect areas of the substrate and then a nucleotide is added to these regions. This technique requires four masks for each layer of nucleotides. While this technique allows for the production of high-density oligonucleotide arrays, it is less efficient than traditional phosphoramidite synthesis chemistry. With efficiencies of about 90 to 95 percent, the percentage of full-length oligonucleotides within a feature is further reduced to about 9 to 27 percent for oligonucleotides that are 25 nucleotides long (0.90^{25} to 0.95^{25}).

Carrico, (US Patent 5,200,313) similarly identifies problematic aspects of hybridization reactions:

1. The purity of the nucleic acid preparation.

2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.

3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.

4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

14. In view of the innumerable art-recognized difficulties, the limited disclosure, and the absence of convincing evidence to the contrary, the pubic would be forced to conduct undue experimentation in order to practice the full scope of the invention, assuming that such a goal could even be attained. Accordingly, claims 80-124 are rejected under 35 USC 112, first paragraph, as not enabled by the disclosure.

Claims 80-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The

specification has been found, at best, to provide only a guide or suggestion as to how the claimed method is to be practiced. The disclosure and indeed the examples do not set forth starting materials and reaction conditions under which a single embodiment can be practiced in full and any meaningful analysis result. While applicant may consider that the written description requirement could be satisfied through assertions of obviousness, such is not dispositive of the instant rejection. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

15. In view of the paucity of the disclosure, and the absence of convincing evidence to the contrary, claims 80-124 are rejected under 35 USC 112, first paragraph, as it relates to written description.

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 80-108 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in Paper No. 2 filed 06 March 2000. In that paper, applicant stated that new claims are being added via a preliminary amendment whereby the claims are drawn to a method and not to a device, and this

statement indicates that the invention is different from what is defined in the claim(s) as al of the original claims were drawn to a device, not a method. Further, a review of the disclosure fails to find support for methods having been considered, at the time of filing, to be the invention. In support of this position, attention is directed to the following portions of the disclosure, starting with the title:

Attorney Docket No.: 18547-009911

PATENT APPLICATION

INTEGRATED NUCLEIC ACID DIAGNOSTIC DEVICE

Inventors:

Page 3:

SUMMARY OF THE INVENTION

The present invention generally provides miniature analytical devices that include a plurality of distinct reaction chambers disposed in a single, miniature body.

Page 6:

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

I. General

It is a general object of the present invention to provide a miniaturized integrated nucleic acid diagnostic device and system. The device of the invention is generally capable of performing one or more sample acquisition and preparation operations, in combination with one or more sample analysis operations. For example, the device can integrate several or all of the operations involved in sample acquisition and storage, sample preparation and sample analysis, within a single, miniaturized, integrated unit. The device is useful in a variety of applications and most notably, nucleic acid based diagnostic applications and *de novo* sequencing applications.

The device of the invention will typically be one component of a larger diagnostic system which further includes a reader device for scanning and obtaining the data from the device, and a computer based interface for controlling the device and/or interpretation of the data derived from the device.

Page 18:

III. The Nucleic Acid Diagnostic System

A. Analytical System

A schematic of a representative analytical system based upon the device of the invention is shown in Figure 1. The system includes the diagnostic device 2 which

Page 19:

B. The Diagnostic Device

As described above, the device of the present invention is generally capable of carrying out a number of preparative and analytical reactions on a sample. To

Page 25:

As described herein, the overall geometry of the device of the invention may take a number of forms. For example, the device may incorporate a plurality of

and

the abstract:

INTEGRATED NUCLEIC ACID DIAGNOSTIC DEVICE

ABSTRACT OF THE DISCLOSURE

The present invention provides a miniaturized integrated nucleic acid diagnostic device and system. The device of the invention is generally capable of performing one or more sample acquisition and preparation operations, in combination with one or more sample analysis operations. For example, the device can integrate

All of the above examples state that the invention lies in the device. While the specification disclose methods of using the device, such teachings are considered an attempt at fulfillment of the enablement requirement under 35 USC 112, first paragraph, and do not imply that applicant, at the time of filing, considered the invention, in whole or in part, to lie in a method of using any device. It is further noted that the subject application was filed on even date with a preliminary amendment yet the declaration filed did not reflect that the subject application was effectively amended, i.e., the instant application was a continuation-in-part. If such had been effected at the time of filing the instant rejection would have been moot. As filed, however, the original disclosure has not been found to support the position that applicant considered method claims to be their invention. Accordingly, and in the absence of convincing evidence to the contrary, claims 80-108 are rejected under 35 USC 112, second paragraph.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 80-110, 112-114, and 116-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilding et al., (US Patent 5,304,487; hereinafter "Wilding 1"), in view of Staecker et al., and Wilding et al., (US Patent 5,587,128; hereinafter "Wilding 2").

22. Wilding 1 discloses a method for analyzing a sample in an integrated microfluidic device that has a plurality of chambers that are in fluid communication with each other. As seen in column 2, the diameter of the channels can range from 0.1 μm to 500 μm. Said channels are in communication with "fluid handling regions." Said regions are considered to meet the limitation of applicants "at least two chambers." Column 3 discloses that the results can be detected through a window, and that such detection includes the use of detectable moieties. Column 9 discloses the optional use of additional components for detecting/viewing the assay results. The aspect that the resultant signal can be viewed through a window is considered to meet the limitation that the "reader" is outside of the chamber (a limitation of independent claims 80 and 93, and claims 81-92, 94-105, 110-124 that depend therefrom).

23. Column 4, first paragraph, teaches explicitly of the optional use of valves within the fluid communication means.

24. The use of the device in the analysis of nucleic acids, be it DNA or RNA is explicitly taught at column 6. The use of detectable moieties in combination with DNA probes, as in nucleic acid assays, is disclosed at column 7.

25. Wilder 1 does not disclose the use of confocal microscopy; nor the use of electrophoretic separation of nucleic acid fragments.

26. Wilding 2, which is based upon a CIP application that matured into Wilding 1, teaches the use of the device in the analysis of nucleic acids, including the amplification of sequences. The use of arrays in concert with the detection of target sequences is disclosed (column 24).

27. While Wilding 2 does teach the sue of readers/detection means that are placed internal to the device, it is also noted that Wilding 2 explicitly teaches that one can detect the signal, e.g., a

fluorescent signal, "either visually or by machine, through a transparent window disposed over the detection region."

28. Wilding 2, column 20, penultimate paragraph, teaches performing electrophoretic separation of nucleic acid sequences. The performance of electrophoretic separation speaks directly to separating the nucleic acid sequences according to size.

29. Wilding 2 does not teach the use of confocal microscopy.

30. Steacker et al., teach of an assay wherein nucleic acids are subjected to amplification and the resultant amplification product is detected/studied through the use of confocal microscopy.

31. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method and device of Wilder 1 and Wilder 2 so to utilize confocal microscopy as taught by Steacker et al. Motivation for performing confocal microscopy on an amplification product is found at page 76, right column, where it is taught that this procedure allows for the detection of minute quantities of mRNA and avoids the time-consuming process of autoradiography.

32. Claims 111 and 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilding 1, Wilding 2, and Staecker et al., as applied to claims 80-110, 112-114, and 116-124 above, and further in view of Brelje et al.

33. Brelje et al., teach at length of the advantages of performing scanning confocal microscopy, including where nucleic acids are being studied. Table 2, column 10, teaches explicitly of DNA specific stains (Chromomycin A3) as well as the use of fluorescein the same fluorophores used by Staecker et al.

34. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Wilder 1, Wilder 2, and Staecker et al., with the method of Brelje et al., so that scanning form of confocal microscopy was used. As set forth in columns 1 and 2, confocal microscopy is well known in the art, yet the aspect of performing scanning confocal microscopy has been found to improve on the design of confocal microscopy. In view of the explicit guidance to use scanning confocal microscopy, and in view of the well-developed nature of confocal microscopy as well as performing nucleic acid assays in integrated microfluidic devices, the ordinary artisan would have been both sufficiently motivated and expectant of success in performing such a combination.

35. For the above reasons, and in the absence of convincing evidence to the contrary, the invention of claims 80-124 is considered to be obvious in view of the prior art of record.

Response to argument

36. At page 4 of the response of19 November 2002, hereinafter the response, applicant asserts that a point of distinction between the claimed invention and that of the prior art is the placement of a valve between the two reaction chambers.

37. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the inclusion of a valve between the two reaction chambers) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

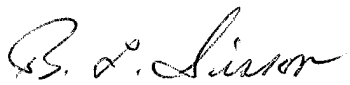
38. Accordingly, and in the absence of convincing evidence to the contrary, the rejection is maintained.

Conclusion

39. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

40. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

41. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
July 9, 2003